PATENT SPECIFICATION

NO DRAWINGS.

851,780

Date of Application and filing Complete Specification: Feb. 13, 1959.

No. 5100/59.

Application made in France on Feb. 25, 1958.

Application made in France on June 7, 1958.

Application made in France on Oct. 2, 1958.

Complete Specification Published: Oct. 19, 1960.

Index at acceptance:—**Classes 2(3)**, B4A2, C3A13A3(A4: B2: H1), C3A13C(1C: 2C: 3C: 10E: 10F); **and 81(1)**, B2S.

International Classification:—**A61k. C07d.**

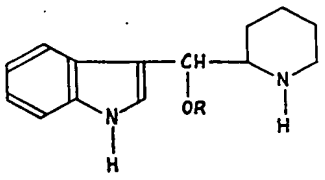
COMPLETE SPECIFICATION

New Indole Derivatives

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate of 21 rue Jean-Goujon, Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to indole derivatives, processes for their preparation and pharmaceutical compositions containing them,

The indole derivatives of the present invention are those of the formula:



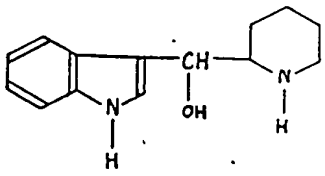
I

(where R represents an alkyl group containing 1 to 5 carbon atoms) and their acid addition salts. Since these compounds contain two asymmetric carbon atoms they may exist in two diastereoisomeric forms, each of these forms being a mixture of enantiomorphs. The syntheses described below in general give a mixture of diastereoisomers which can be separated by conventional methods; a single pure diastereoisomer is usually obtainable by recrystallisation of the mixture from a suitable solvent.

The indole derivatives of the invention are particularly potent diuretics. They also have the advantage of not affecting unfavourably the sodium/potassium balance in the organism. The various isomeric forms differ in degree of activity, though all possess useful diuretic properties. The more active diastereoisomers are those of higher melting point, obtainable by carrying out the etherification process described below at about 50° C. The other less active diastereoisomers may be converted into the more active diastereoisomers by treatment with a solution of hydrogen chloride in an alcohol of formula ROH (where R is as hereinbefore defined) at between 20° and 50° C. The alcohol used in this conversion should be one in which the alkyl group R is the same as the alkyl group R of the ether being treated.

The preferred compounds of the invention are the diastereoisomer of (3-indolyl)(2-piperidyl)methoxymethane which melts at about 157° C. and its acid addition salts.

According to a feature of the invention the aforesaid new indole derivatives are prepared by a process which comprises etherifying the compound:



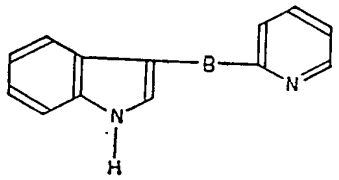
II

with an alcohol ROH (where R is as hereinbefore defined). Preferably the compound of formula II is reacted with the alcohol of formula ROH in the presence of hydrogen chloride previously dissolved in the said alcohol. If the reaction is carried out at about 50° C. or at below 5° C. a predominating proportion of the one or the other diastereoisomer is obtained. As already stated, the diastereoisomers formed at about 50° C. have greater diuretic activity than those formed at below 5° C.

According to a further feature of the invention the indole derivatives of general formula I are prepared by reducing with hydrogen in the presence of Adams' platinum and in an alcoholic or aqueous alcoholic medium, where the alcohol is of formula ROH (where R is as hereinbefore defined), a compound of formula;

[*Price 3s. 6d.*]

BEST AVAILABLE COPY



III

(wherein B represents a >CO, >CHOH, or >CHOR group, where R is as hereinbefore defined). This reduction may be carried out at room temperature and atmospheric pressure, but preferably pressures above atmospheric and below 100 kg./cm² are used.

The acid addition salts of the compounds of general formula I may be obtained from the corresponding bases by known methods for the conversion of bases to acid addition salts.

The expression "known methods" as used in this specification and in the appended claims means methods heretofore used or described in the chemical literature.

When the compounds of general formula I are used for therapeutic purposes in the form of acid addition salts, it should be understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions; in other words, only non-toxic salts are contemplated. Suitable acid addition salts include hydrohalides (for example hydrochlorides), phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methane sulphonates and ethane disulphonates.

The following Examples illustrate the invention.

Example I

3-Picolylindole hydrochloride (50 g.) is dissolved in methanol (1,150 cc.) and water (115 cc.). The solution obtained is hydrogenated under ordinary pressure and temperature in the presence of Adams' platinum (platinum oxide (10 g.) reduced with hydrogen). In 6 hours the reaction ceases (4 molecules of hydrogen absorbed for 1 molecule of hydrochloride used).

The catalyst is separated by filtration and the filtered solution is dried under reduced pressure (15 mm. Hg.). The residue (52 g.) is dissolved in distilled water (300 cc.) in the presence of anaesthetic ether (250 cc.), and the solution obtained is made alkaline with sodium hydroxide (d = 1.33, 20 cc.) and then agitated until there are obtained two clear layers. The organic solution is decanted and the alkaline solution is washed with anaesthetic ether (100 cc.). The ethereal solutions are collected and dried over anhydrous potassium carbonate.

The residue (40 g.) obtained by evaporation of the ether on a water-bath is treated with boiling ethyl acetate (120 cc.). After cooling, separation, washing with ethyl acetate (3 × 10 cc.) and then drying *in vacuo*, there is obtained (3 - indolyl)(2 - piperidyl)methoxymethane (24.5 g.), melting at 146—147° C. The product is purified by recrystallisation from methyl ethyl ketone and then melts at 156—157° C.

The hydrochloride of 3-picolylindole, which melts at 178—180° C., is prepared by the action of a solution of hydrochloric acid in ethanol on 3-picolylindole dissolved in methyl ethyl ketone.

Example II

3-Picolylindole hydrochloride (420 g.) is dissolved in a solution of methanol (9.65 l.) and distilled water (0.965 l.). The solution obtained is hydrogenated at ordinary pressure and temperature in the presence of Adams' platinum (84 g.). Hydrogenation is complete at the end of 8 hours.

The catalyst is filtered off and washed with water (100 cc.) and the filtrate is concentrated *in vacuo*. The oily residue is treated with water (2.5 l.) and anaesthetic ether (2 l.) and made alkaline with 10 N sodium hydroxide (175 cc.). The free base dissolves in the ether as it is formed. The ethereal solution is decanted and the aqueous portion is washed with ether (500 cc.). The ethereal solutions are combined and left for 3 hours at room temperature. Crystals form and are separated, washed with ether (3 × 100 cc.) and dried *in vacuo*. There is obtained a product (65 g.) which melts at 204—205° C. After recrystallisation from a 70% aqueous solution (1050 cc.) of *iso*propanol, there is obtained (3-indolyl)(2-piperidyl)methanol (47.4 g.), which melts at 213—214° C.

The ethereal solution obtained by filtration of the preceding crude product is dried over anhydrous potassium carbonate and after evaporation there remains an oily residue (304 g.) which is treated with hot ethyl acetate (900 cc.). After cooling, crystals form which are separated, washed with ethyl acetate (150 cc. in 3 lots) and then dried *in vacuo*. There is obtained a product (140 g.) melting at 150—151° C. After recrystallisation from methyl ethyl ketone, passage over a column of alumina of a solution in ethyl acetate, then final crystallisation from the same solvent, there is obtained (3 - indolyl)(2 - piperidyl)methoxymethane (82 g.), melting at 156—157° C.

By concentration of the ethyl acetate filtrates there is isolated a crystalline mixture melting at 125—128° C. which contains 3-(2-piperidylmethyl)indole (50%) and (3-indolyl)-(2-piperidyl)methoxymethane (30%). The 3-(2-piperidylmethyl)indole is separated as the picrate in acetone; this picrate melts at 220° C. After treatment with lithium hydroxide and recrystallisation from ethyl acetate there

BEST AVAILABLE COPY

is isolated 3-(2-piperidylmethyl)indole (34 g.) melting at 159° C.

By evaporation of the acetone from the mother liquors of the crystallisation of the picrate, treatment of the residue with lithium hydroxide and recrystallisation, there is isolated crude (3-indolyl)(2-piperidyl)methoxymethane (28 g.), m.p. 150° C., which is purified by passage over alumina.

EXAMPLE III

(3-Indolyl)(2-piperidyl)methanol (11.5 g.), m.p. 213—214° C., is treated with anhydrous methanol (150 cc.) and an ethereal solution (15 cc.) containing 4 moles of hydrogen chloride per litre (4N ethereal hydrogen chloride). The solution obtained is heated under reflux for 30 minutes on a boiling water bath and neutralised to pH 6—7 with diethylamine and the solvents are evaporated. The residue is treated with water (100 cc.), 5N sodium hydroxide (25 cc.) and anaesthetic ether (100 cc.). The ether is decanted and the aqueous solution is washed with ether (50 cc.). The ethereal solutions are combined and dried over anhydrous potassium carbonate. The ether is evaporated and the residue (13 g.) is treated with ethyl acetate (45 cc.) under reflux. After cooling, crystals form which are separated and washed with ethyl acetate (10 cc.). There is obtained after drying *in vacuo* crude (3-indolyl)(2-piperidyl)methoxymethane (2.85 g.), m.p. 144° C.

The filtrate is concentrated, treated with anhydrous methanol (115 cc.) and 4N ethereal hydrogen chloride (11.5 cc.). After 30 minutes under reflux and treating as above there is isolated a crude product (1.90 g.), melting at 143° C.

By a third treatment of the residue of the preceding treatment with anhydrous methanol (90 cc.) and 4N ethereal hydrogen chloride (9 cc.) there is isolated a crude product (1.52 g.) melting at 143° C.

By a fourth treatment of the residue with anhydrous methanol (60 cc.) and 4N ethereal hydrogen chloride (6 cc.), there is isolated a crude product (0.67 g.), melting at 143° C.

In all there are isolated 6.94 g. of the crude product. After recrystallisation from methyl ethyl ketone and passage over alumina of a solution of the product in ethyl acetate, there is obtained pure (3-indolyl)(2-piperidyl)methoxymethane, m.p. 156—157° C.

EXAMPLE IV

(3-Indolyl)(2-pyridyl)methanol (4.48 g.) is dissolved in anhydrous methanol (100 cc.) and the solution is brought to pH 2 by the addition of a 9N solution of hydrogen chloride in methanol. The solution is left for 30 minutes at room temperature and is then hydrogenated in the presence of Adams' platinum at ordinary pressure and temperature. The hydrogenation is complete in 2 hours.

The catalyst is filtered off and washed with methanol (20 cc.). The solvents are evaporated on a boiling water bath. The residue is treated with water (100 cc.), 5N sodium hydroxide (10 cc.) and ether (100 cc.). The ethereal solutions are combined, dried over anhydrous potassium carbonate and evaporated. The oily residue (4.8 g.) is treated with hot ethyl acetate (15 cc.) and, on cooling, crystals are formed which are separated, washed with ethyl acetate (4 cc.) and dried *in vacuo*. There is obtained crude (3-indolyl)(2-piperidyl)-methoxymethane (2.1 g.), m.p. 150° C. The product, when purified by passage of a solution of the product in ethyl acetate over alumina and re-crystallisation from the same solvent, melts at 156—157° C.

EXAMPLE V

(3 - Indolyl)(2 - pyridyl)methoxymethane (5 g.) is treated with anhydrous methanol (50 cc.) and with a solution of hydrogen chloride in methanol containing 8.3 moles of hydrogen chloride per litre of solution so that the pH of the reaction medium is 1—2 (estimated with indicating paper). The solution obtained is introduced into a 250 cc. autoclave with Adams' platinum (0.9 g.). It is hydrogenated at room temperature, under an initial hydrogen pressure of 50 kg/cm². The pressure falls to 43 kg/cm² in 10 minutes and does not vary for the next 15 minutes. The catalyst is then filtered off, the methanol is evaporated *in vacuo* and the residue is treated with water (20 cc.), ether (50 cc.) and concentrated sodium hydroxide (d = 1.33, 5 cc.). The ethereal solution is decanted, washed with water (20 cc.) and dried over anhydrous potassium carbonate. After evaporation of the ether, the semi-crystalline residue (4.6 g.) is treated with boiling ethyl acetate (20 cc.).

On cooling at 0° C. for 5 hours copions crystallisation occurs. The crystals are separated, washed and dried and there is obtained (3-indolyl)(2-piperidyl)methoxymethane (3.3 g.), m.p. 154° C. The product is purified by recrystallisation from methyl ethyl ketone and then melts at 157° C.

(3 - Indolyl)(2 - pyridyl)methoxymethane is prepared by the action of methanolic hydrogen chloride on cold (3-indolyl)(2-pyridyl)methanol. The product, purified by crystallisation from ethyl acetate, melts at 126° C.

EXAMPLE VI

(3 - Indolyl)(2 - pyridyl)methanol (128 g.) with one molecule of methanol of crystallisation is treated with anhydrous methanol (1300 cc.) and with a solution of hydrogen chloride in methanol (7.4 mol. of hydrogen chloride per litre of solution) in sufficient quantity for the pH of the reaction medium to be 1—2 (estimated with indicating paper). The solution obtained is treated with charcoal, filtered and left for one hour at room temperature. It is then hydrogenated in a 5 litre autoclave, in the presence of Adams' platinum (23 g.) at room temperature under an initial hydrogen pressure of 50 kg/cm². The pressure falls to

BEST AVAILABLE COPY

40 kg/cm² in five minutes. The reaction is left to continue for another 15 minutes without change of pressure. The catalyst is then filtered off and the pale yellow solution obtained is evaporated *in vacuo*. The residue is treated with water (150 cc.), chloroform (350 cc.) and concentrated sodium hydroxide solution (d = 1.33, 60 cc.). The chloroform layer is decanted and washed with water (2 × 100 cc.). After evaporation of the chloroform, the oily residue (170 g.) is dissolved in boiling ethyl acetate (450 cc.). On cooling at 0° C. for 3 hours copious crystallisation occurs. The crystals are separated and washed with ethyl acetate (3 × 25 cc.). After drying there is obtained a product (98.8 g.), m.p. 154° C. The product is purified by recrystallisation from methyl ethyl ketone (280 cc.) and there is thus obtained (3-indolyl)(2-piperidyl)-methoxymethane (83.5 g.), m.p. 157° C.

EXAMPLE VII

(3 - Indolyl)(2 - piperidyl)methanol (10. g.), m.p. 214° C., is added in small portions over 20 minutes to a mixture containing anhydrous methanol (110 cc.) and ethereal hydrogen chloride (6 cc.) (containing 5.4 mol. of hydrogen chloride per litre of solution) maintained at 4° C. The solution obtained is agitated for 1 hour at 2° C. and then neutralised with pure diethylamine. The solvents are evaporated *in vacuo* and the residue is treated with water (100 cc.), ether (100 cc.) and 5N sodium hydroxide (10 cc.). The ethereal solution is decanted, dried over anhydrous potassium carbonate and evaporated.

The oily residue (10.1 g.) is dissolved in a mixture (500 cc.) of 1 volume of benzene and 2 volumes of *cyclo*hexane. The solution obtained is chromatographed over a column of alumina (150 g.) of 2.7 cm. diameter. It is eluted with the preceding mixture (2 litres) and then with a mixture of 1 volume of benzene to 1 volume of *cyclo*hexane.

The eluates are combined and evaporated. The oily residue (4.1 g.) is dissolved in ethanol (10 cc.) treated with a solution of fumaric acid (0.975 g.) in boiling ethanol (15 cc.). A neutral fumarate crystallises while hot. After cooling for 2 hours at 0° C. the crystals are separated, washed with ethanol and dried. There is obtained the neutral fumarate of (3-indolyl)(2-piperidyl)methoxymethane (4 g.), m.p. 255° C., diastereoisomeric with the product described in the previous Examples, the neutral fumarate of which melts at 246° C.

EXAMPLE VIII

Anhydrous ethanol (285 cc.) is added to (3 - indolyl)(2 - piperidyl)methanol (22 g.), m.p. 214° C. The product remains in suspension on agitation. There is added dropwise ethanolic hydrogen chloride (containing about 6 mol. of hydrogen chloride per litre of solution) until the pH of the reaction medium is about 1—2 (estimated with indicating paper). The aminoalcohol in suspension dissolves and there is obtained a pale pink solution. The reaction products are heated at 40° C. on a water bath for 30 minutes. The solution obtained is then neutralised with an excess of pure diethylamine and the ethanol is evaporated *in vacuo*. The residue is treated with water (100 cc.), and ether (100 cc.) and there is added an excess of concentrated sodium hydroxide so that the aqueous solution is at pH 14. The aqueous layer is decanted and again extracted with ether (50 cc.). The ethereal solutions are combined and dried over anhydrous potassium carbonate and evaporated.

The oily residue (26 g.) is dissolved in *iso*propyl ether (150 cc.). On cooling at 0° C. for 18 hours a product crystallises. The crystals are separated and washed with *iso*propyl ether (3 × 10 cc.). After drying *in vacuo* there is obtained a product (14.8 g.), m.p. 157—158° C.

There is obtained by recrystallisation from ethyl acetate (60 cc.) (3-indolyl)(2-piperidyl)-ethoxymethane (11.5 g.), m.p. 160—161° C.

EXAMPLE IX

(3-Indolyl)(2-piperidyl)methanol (11.5 g.), m.p. 214° C., is treated with propanol (150 cc.) and ethereal hydrogen chloride (11.5 cc.), containing 5.4 mol. of hydrogen chloride per litre of solution. The yellow solution obtained is left for 30 minutes at room temperature, then neutralised with pure diethylamine and the propanol is evaporated *in vacuo*. The residue is treated with water (100 cc.), ether (100 cc.) and 5N sodium hydroxide (10 cc.). The aqueous layer is decanted and extracted again with ether (50 cc.). The ethereal solutions are combined and dried over anhydrous potassium carbonate. The ether is evaporated on a water-bath and the residue (13.5 g.) is treated with boiling ethyl acetate (40 cc.). On cooling at 0° C. for 3 hours, copious crystallisation occurs. The crystals are separated, washed and dried. There is obtained crude (3-indolyl)(2-piperidyl)propoxymethane (7.5 g.), m.p. 149—150° C.

This product, purified by recrystallisation from ethyl acetate, melts at 150° C.

EXAMPLE X

(3 - Indolyl)(2 - piperidyl)methanol (10 g.), m.p. 214° C., is treated with *iso*propanol (30 cc.) and ethereal hydrogen chloride (11.5 cc.) containing 4 mol. of hydrogen chloride per litre of solution. The yellow solution obtained is left for 1 hour at room temperature, then neutralised with pure diethylamine. The *iso*propanol is evaporated *in vacuo* and the residue is treated with water (100 cc.), ether (100 cc.) and 5N sodium hydroxide (10 cc.). The aqueous solution is decanted and extracted again with ether (50 cc.). The ethereal solutions are combined and dried over anhydrous potassium carbonate. The ether is evaporated and the residue (13 g.) is treated with boiling ethyl acetate (56 cc.). There remains a small

BEST AVAILABLE COPY

amount of insoluble matter which is filtered off while hot and the filtrate is concentrated to 30 cc. On cooling overnight at 0° C., copious crystallisation occurs. The crystals are separated, washed and dried. There is then obtained a product (7.8 g.) which melts at 164° C. By recrystallisation from methyl ethyl ketone (26 cc.), there is obtained pure (3 - indolyl)(2 - piperidyl)*iso*propoxymethane (4 g.), melting at 169—170° C.

EXAMPLE XI

(3 - Indolyl)(2 - piperidyl)methanol (8 g.), m.p. 214° C., is treated with butanol (100 cc.) and ethereal hydrogen chloride (8 cc.), containing 5.4 mol. of hydrogen chloride per litre of solution. The yellow solution obtained is left for 30 minutes at room temperature, then neutralised with pure diethylamine. The butanol is evaporated *in vacuo* and the residue is treated with water (100 cc.), ether (100 cc.) and 5N sodium hydroxide (10 cc.). The ethereal solution is decanted and dried rapidly over anhydrous potassium carbonate. The ether is evaporated and the residue (11 g.) crystallises. It is then treated with boiling ethyl acetate (50 cc.). On cooling for 2 days at 0° C. copious crystallisation occurs. The crystals are separated, washed and dried. There is obtained a product (7.4 g.), melting at 158—159° C. By recrystallisation from ethyl acetate (50 cc.), there is obtained pure (3 - indolyl)(2 - piperidyl)butoxymethane (6.3 g.), m.p. 159° C.

The present invention further includes within its scope pharmaceutical compositions which comprise one or more compounds of general formula I or their acid addition salts as aforesaid together with a significant amount of a pharmaceutical carrier. The invention includes especially such compositions made up for oral or parenteral administration. In clinical practice the compounds of the present invention will normally be administered orally so that compositions suitable for oral administration are preferred.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds of general formula I is or are admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening and flavouring agents.

The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the active substances of general formula I with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

Suitable pharmaceutical compositions according to the present invention are illustrated in the following Examples.

EXAMPLE XII

250 mg. Tablets are formed with the composition:—

(3-indolyl)(2-piperidyl)methoxymethane	250 mg.
starch	232 mg.
colloidal silica (desiccated)	100 mg.
magnesium stearate	18 mg.

These tablets can be used at a dose of 1 or 2 a day.

EXAMPLE XIII

250 mg. Enteric-coated tablets are formed with the composition:—

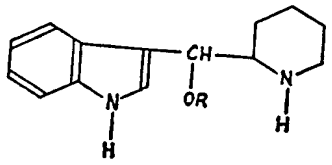
(3-indolyl)(2-piperidyl)methoxymethane	250 mg.
starch	147 mg.
colloidal silica (desiccated)	68 mg.
magnesium stearate	17 mg.

The tablets obtained are covered with sugar and then coated with a layer of a mixture of cellulose acetate phthalate and pelmitic acid.

WHAT WE CLAIM IS:—

1. Indole derivatives of the general formula:

BEST AVAILABLE COPY

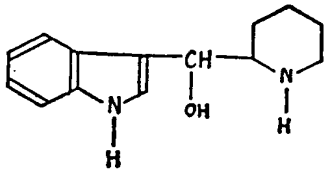


(wherein R represents an alkyl group containing 1 to 5 carbon atoms) and their acid addition salts, in the form of pure diastereoisomers or mixtures of diastereoisomers.

2. The higher melting diastereoisomers of the indole derivatives claimed in claim 1 and their acid addition salts.

3. The diastereoisomer of (3-indolyl)(2-pieridyl)methoxymethane which melts at about 157° C. and its acid addition salts.

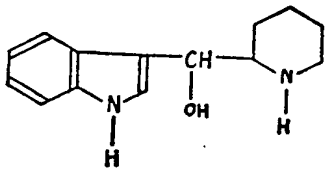
4. A process for the preparation of an indole derivative as claimed in claim 1 or 2 which comprises etherifying the compound of formula:



with an alcohol of formula ROH, where R is as defined in claim 1.

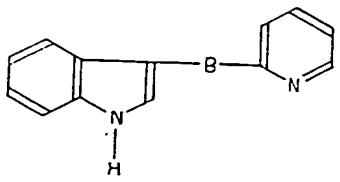
5. A process according to claim 4 wherein the etherification is carried out with a solution of hydrogen chloride in an alcohol of formula ROH (where R is as defined in claim 1).

6. A process for the preparation of a compound as claimed in claim 2 which comprises reacting the compound of formula:



with an alcohol of formula ROH (where R is as defined in claim 1) in the presence of hydrogen chloride at about 50° C.

7. A process for the preparation of an indole derivative as claimed in claim 1 or 2 which comprises reducing a compound of the formula:



(where B represents a >CO, >CHOH, or >CHOR group, where R is as defined in claim 1) with hydrogen in the presence of Adams' platinum and in an alcoholic or aqueous alcoholic medium where the alcohol is of formula ROH, R being as defined in claim 1.

8. Process for the preparation of an indole derivative as claimed in any of claims 1 to 3 substantially as described in any one of Examples I to XI.

9. Indole derivatives as claimed in claim 1 when prepared by a process claimed in any one of claims 4 to 8.

10. A pharmaceutical composition comprising at least one indole derivative as claimed in any of claims 1 to 3 and 9 in association with a significant amount of a pharmaceutical carrier.

11. A pharmaceutical composition as claimed in claim 10 substantially as described in either of the foregoing Examples XII and XIII.

J. A. KEMP & CO.,
Chartered Patent Agents,
9 Staple Inn, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1960.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

BEST AVAILABLE COPY